INFLAMMATORY BOWEL DISEASE

Adult height in patients with early onset of Crohn's disease

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Gut 2002;**51**:26–29

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Accepted for publication 2 October 2001

Background: Growth impairment during childhood and adolescence is a common problem faced by patients with an early onset of Crohn's disease.
Aims: To establish how the final adult height is affected in patients with early onset of symptoms of Crohn's disease.
Methods: Information on height, parental height, and disease history was obtained from 135 patients with Crohn's disease who reached their adult height (men 22–40 years, women 18–40 years) using a questionnaire and by outpatient measurement of height where possible. Subsequently, adult heights were expressed as standard deviation scores, with and without correction for the expected target height.
Results: Patients with onset of disease before puberty were shorter compared with patients with onset in adulthood ($p<0.01$). This difference was not statistically significant when adult heights were corrected for parental height. Also, height standard deviation scores for those patients with onset of disease before puberty were significantly lower than those with onset of disease during puberty ($p<0.05$) but after correction for parental height the difference was not significant. The site of disease had no influence on adult height. Patients who had used corticosteroids during puberty were significantly shorter than patients who had not ($p=0.005$). This was also true when corrected for target height ($p=0.007$).
Conclusions: Although there was a trend indicating a deficit in adult height in patients with an early onset of Crohn's disease, once adjustment was made for parental height, this difference was not significant. Use of corticosteroids in puberty resulted in lower adult height.

Paediatric inflammatory bowel disease is often accompanied by growth retardation, as evidenced by deviations from growth velocity curves and height for age curves.[1 2] Bone age can also be retarded. The prevalence of growth retardation during childhood and adolescence for patients with inflammatory bowel disease ranges between 13% and 58%, although much higher values have also been reported,[1–5] and it is apparent that this problem is more commonly encountered in Crohn's disease than in ulcerative colitis.[1–6] The major longitudinal effects on growth reduction have been demonstrated in Tanner stages I and II.[2 4 7] In contrast, Ferguson and Sedgwick[8] found no growth retardation in teenagers but in this study 18 girls were postmenarchal when initially diagnosed so no decrease in height would be expected.

The exact mechanisms by which growth impairment occurs are unclear. The aetiology of growth impairment in inflammatory bowel disease is multifactorial. Both inadequate caloric intake and circulating cytokines from intestinal inflammation have major detrimental effects on growth. Malnutrition as well as inflammation suppress insulin-like growth factor 1 production, which plays a pivotal role in postnatal growth.[9–13]

It has often been stated that corticosteroids have a negative effect on growth but recent studies have revealed that the disease activity itself has a larger impact on linear growth than the use of steroids.[1 14] In another study in which two groups of boys with Crohn's disease treated with alternate day prednisone therapy (0.3 mg kg >3 months per year) were compared with minimal alternate day prednisone therapy (<3 months per year) over two years, it was found that both regimens had no effect on linear growth.[15]

Most of these theories and findings are restricted to children and adolescents with Crohn's disease and the consequences for adult height require further investigation. Our aim was to clarify the inconsistencies found in the literature regarding final adult height by studying 135 Dutch patients with childhood onset Crohn's disease who had reached adulthood.

PATIENTS AND METHODS

Originally, 261 patients between the ages of 18 and 40 years, known at the department of gastroenterology-hepatology at Leiden University Medical Centre with a diagnosis of Crohn's disease were selected to complete a questionnaire. All patients had visited the department of gastroenterology-hepatology at least once and the diagnosis of Crohn's disease was made based on clinical, radiological, endoscopic, and/or histological findings. Questionnaires were received by 242 patients whose most current address was available at the hospital administration.

The questionnaire requested information on: age at onset of symptoms, age at diagnosis, use of corticosteroids, age at start and cessation of therapy with corticosteroids, parental height and age, initial localisation of disease, and ethnic background. Patients were instructed to perform four measurements of their own height and their parent's height at home.

When no direct information was available for the parent's height, their height as stated in their passport was used. The height of 29 patients who visited the outpatients department within a period of approximately three months was measured by one observer (NA) using a wall mounted stadiometer in order to confirm the home measurements. Three measurements were made and the average was used for all further

Abbreviations: SDS, standard deviation scores; H-SDS, height SDS.

Table 1 Number of patients, sex, height-standard deviation scores (SDS), and height minus target height (Δheight) in each group according to age at onset of Crohn's disease

Group	n	Sex (M:F)	Height-SDS	ΔHeight (cm)
Prepubertal	15	8:7	–0.91(1.24)	–2.11(5.68)
Pubertal	49	24:25	–0.10(1.09)	0.61(5.63)
Adult	71	13:58	0.07(0.95)	0.88(6.01)

analyses. Once the questionnaires were received, they were reviewed so as to categorise patients into groups according to age at onset of symptoms and sex. Subsequently the information was checked in the patient files.

Three groups were made:

- Men with onset of symptoms before the age of 13 years and women with onset of symptoms before the age of 11 years were considered to be prepubertal.
- Men with onset of symptoms between the ages of 13 and 22 years and women with onset of symptoms between the ages of 11 and 18 years were considered to be pubertal.
- Men with onset of symptoms after the age of 22 years and women with onset of symptoms after the age of 18 were considered to be adults.

Information on parental height was used to determine the expected target height of the patient based on genetic factors using the following formulae[16]:

For men:

Target height=[(father's height+mother's height+12)/2]+3 (in cm)

For women:

Target height=[(father's height+mother's height–12)/2]+3 (in cm)

In order to make a comparison between the patient groups and the general Dutch population, standard deviation scores (SDS) for height were calculated using the following formula[17]:

height SDS (H-SDS)=(observed height–mean height for age and sex of general population)/SD for age and sex of the general population.

Values for mean height and SD of height for the adult Dutch population were as follows:

For men: mean height=182.0 cm, SD=6.7 cm

For women: mean height=168.3 cm, SD=6.2 cm.[17]

Deficits from calculated target height were calculated as follows:

ΔHeight=observed adult height–target height.

The height measurements at home were compared with those performed at the outpatients clinic by calculating the difference in cm and determining Pearson's correlation coefficient. Differences between groups of measurements were analysed by ANOVA or the Student's *t* test. Stepwise multiple regression analysis was used to find the most important predictor for height SDS and Δheight of the patients. Age at the start of the complaints, sex, site of the disease, and use of corticosteroids before or during puberty were included into the models as predictors.

RESULTS

Of the 261 patients approached, 242 had received the questionnaire and 146 of these responded (=60%). After reviewing the questionnaires as well as the patients' records, 135 patients were included in the analysis (55.8%). Of the patients not included, one had been treated for accelerated growth during puberty, one was suffering from a serious ankylosing spondylitis (thus preventing accurate height measurements), five patients were of non-Dutch origin, and nine patients had returned incomplete questionnaires. On the other hand, accurate information by telephone or by personal contact was available from five patients who had not replied by returning the questionnaire. Once these patients were categorised into groups, the numbers shown in table 1 were obtained. In order to ensure that the measurements performed at home were accurate, a comparison was made between home measurements as stated on the questionnaires and those performed at the outpatients clinic. Pearson's correlation coefficient was 0.994, with a mean difference of 0.016 cm for the 29 patients (21%) measured both at home and at the outpatients clinic. The mean absolute fault (the difference between home measurements and clinic measurements) was 0.54 cm (minimum 0; maximum 3.5 cm; SD 0.66) (fig 1). Therefore, home measurements for height were used for all further analyses.

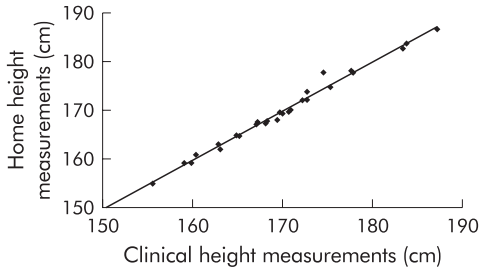

Figure 1 Correlation between home height measurements and clinical height measurements (r^2=0.994).

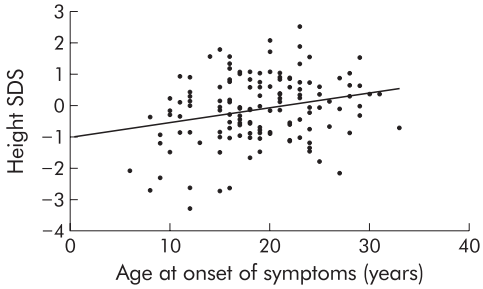

Figure 2 Relationship between height standard deviation scores (SDS) and age at onset of symptoms (r^2 =0.0623, p<0.0001).

Age at onset and final adult height

The ANOVA test revealed a significant difference (p<0.005) in H-SDS between the three age groups. The calculated H-SDS for patients with onset of symptoms before the start of puberty was significantly lower than the H-SDS for those with symptoms on reaching adulthood (p<0.01) and also lower than for their counterparts with start of symptoms during puberty (p<0.05). Adult H-SDS values as a function of onset of symptoms are shown in fig 2 (r^2=0.0623; p<0.0001). H-SDS for patients with symptoms during puberty was not significantly lower than for patients with onset of symptoms in adulthood. The deviation from the target height (Δheight) did not reach statistical significance in the three different age groups (table 1).

Disease site and final adult height

Thirty nine patients (29%) had initial disease localisation limited to the colon only. Another 39 (29%) had localisation limited to the ileum only, with the remaining 57 (42%) having

lesions spread over the ileum and colon. The disease site had no influence on adult height (ANOVA).

Use of corticosteroids and adult height

From the total patient group, 27 patients had received corticosteroid treatment during or before puberty (men below the age of 22 years and women below the age of 18 years). Eight patients had used corticosteroids before puberty while 19 had used them during puberty. The use of corticosteroids during or before puberty seems to be of crucial importance for adult height. Patients with disease onset during puberty with concomitant use of corticosteroids were significantly shorter than patients with onset of symptoms in the same group who did not use corticosteroids ($p=0.03$).

Finally, multiple regression analysis was performed on the data, implicating corticosteroid use as the only factor to have a negative influence on both H-SDS and deviations from target height (Δheight) ($p=0.005$ and $p=0.007$, respectively).

Extra feeding and surgery

The influence of tube feeding and/or total parenteral nutrition in our patients could not be estimated because the period in which patients in the prepubertal group had their first complaints was too long ago. For most patients no such therapy was available at that time. For men it was between 10.8 and 28.1 years previously (in seven more than 15 years); for women it was between 13.5 and 29.7 years previously (in five more than 15 years).

Only three male patients had a bowel resection between the ages of 13 and 15 years. All women had a bowel resection but only two had surgery, at ages 14 and 16 years, respectively. All other operations were performed after the age of 18 years and hence the numbers were too small for analysis.

DISCUSSION

Relatively few studies have been published on final adult height of patients with Crohn's disease and conflicting results have been presented. Hildebrand and colleagues[18] stated that 29% of patients with Crohn's disease reached a final adult height <1.0 SDS whereas Ferguson and Sedgwick[8] found that 67 of 70 patients with inflammatory bowel disease (of which 50 had Crohn's disease) achieved a normal adult height. Markowitz and colleagues[2] found an overall deficit in adult height of 37% (14 of 38 patients) in patients with Crohn's disease, measured by two or more different methods. Prospective studies among particular groups of children or adolescents with either Crohn's disease or ulcerative colitis demonstrated that the prevalence of growth retardation falls as patients approach adulthood, implying that there is evidence of a "catch up" growth to some extent.[2 18] This concept can in part be explained by the effects of different forms of therapy as it has been demonstrated that there is an increase in growth velocity during periods of remission, as induced by an elemental diet, parenteral nutrition, or intestinal resection.[14 19–21] Because in the present study the pubertal stage was based solely on patient age and not on Tanner stage, a difference between the "prepubertal" and "pubertal" effect on growth cannot be stated with accuracy. However, the fact that puberty is often delayed in inflammatory bowel disease could only indicate that some prepubertal patients would have been falsely included in the "pubertal" group. If prepubertal status is a negative predictor for final height, this would then lead to a lowering of final height in the "pubertal" group.

In this study we have demonstrated that there is a trend indicating the presence of lower values for adult height in patients with a relatively early onset of disease. However, these patients did not show a significant deviation from their target height (mid parental height corrected for sex and secular trend). This could imply that there is a familial basis for the observed short stature not related to Crohn's disease, a factor which is often overlooked in other studies. As patients and parents measured their own height, some errors in height are possible. To determine if their self measured length was correct, height was also measured at the outpatients clinic in a small group of patients. "Home measured height" and "outpatient clinic height" measured by one person correlated well.

In our study localisation of disease did not seem to influence adult height although in a recent study McCartney *et al* contradicted these findings claiming that linear growth was related to the site of disease.[22] In their study they noticed that the largest difference between observed height and mid parental height was in the group of patients with disease limited to the small bowel.

Corticosteroid use during puberty seems to influence adult height in a negative manner. When data were analysed in a multiple regression model, use of corticosteroids in puberty was the only factor influencing adult height in these patients. Because this was a retrospective study, some errors may have been made in the exact year of corticosteroid use. A lower adult height could also be caused by a more serious disease in which steroids were needed. Because no information on disease activity was available, the relation with adult height could not be made. However, in most cases the time period of corticosteroid use was confirmed in the patient files. Griffiths and colleagues[6] demonstrated that use of prednisolone was not a significant predictor of height velocity and that the major influencing factor was the severity of gastrointestinal symptoms. Height velocity decreased with increasing gastrointestinal symptoms during the first two years after diagnosis.

The effects of chronic use of corticosteroids has been described in more detail in young patients with asthma. Silverstein *et al* found no significant difference between adult height in patients with glucocorticoid treatment and adult height of those who had not received glucocorticoids during childhood.[23] A possible explanation is that children with asthma generally use lower doses of steroids than children with active Crohn's disease. Moreover, asthmatic children predominantly use inhalers, with steroid administration by inhalation.

Regarding adult height, the results of this study portray a trend indicating a disadvantage of patients with an early onset of Crohn's disease compared with patients with a late onset of disease. Moreover, use of corticosteroids in puberty has a significant negative effect on adult height. It is conceivable that the results of this study have implications for the treatment of patients with Crohn's disease in puberty. Prescription of steroids in puberty should be avoided as much as possible and alternative therapies should be considered.

A larger patient population combined with adequate data on parental height and precise data on corticosteroid regimens would further clarify the findings of a relatively decreased adult height. Additionally, more prospective studies are necessary and must be undertaken in national or international studies.

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